Respiratory Medicine (2006) **100**, 2177–2182

ELSEVIER

respiratoryMEDICINE

Genetic and environmental contributions to hay fever among young adult twins

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Received 6 September 2005; accepted 14 March 2006

KEYWORDS
Environment;
Genetics;
Hay fever;
Twin study

Summary
Background: The susceptibility to develop hay fever is putatively the result both of genetic and environmental causes. We estimated the significance and magnitude of genetic and environmental contributions to hay fever among young adult twins.
Methods: From the birth cohorts 1953–82 of The Danish Twin Registry 11,750 twin pairs were identified through a nationwide questionnaire survey. Subjects were regarded hay fever cases when responding affirmatively to the question 'Do you have, or have you ever had hay fever?' Latent factor models of genetic and environmental effects were fitted to the observed data using maximum likelihood methods.
Results: The overall cumulative prevalence of hay fever was 12.6%. Identical twins were significantly more likely to be concordant for hay fever than were fraternal twins ($P<0.001$). Additive genetic effects accounted for 71% and non-shared environmental effects accounted for 29% of the individual susceptibility to hay fever. The same genes contributed to the susceptibility to hay fever both in males and in females. In families with asthma, the susceptibility to develop hay fever was, in addition to genes, to a great extent ascribable to family environment, whereas the aetiology of 'sporadic' hay fever was mainly genetic.

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0954-6111/$ - see front matter
doi:10.1016/j.rmed.2006.03.013

Conclusions: The susceptibility to develop hay fever is attributable to major genetic influences. However, effects of family environment and upbringing are also of importance in families where asthma is present. These results indicate that different sub-forms of hay fever may have different aetiologies.

Introduction

Hay fever is a disease of the airways, which is characterised by sneezing, itching, rhinorrhea, and nasal congestion often following exposure to aeroallergens.[1] In a variable number of cases raised blood levels of IgE and atopic sensitisation to specific allergens accompany it.[2] Hay fever is associated with asthma and atopic dermatitis and this phenotypic overlap is known to be to a great extent genetic in origin.[3,4] Hay fever affects an extensive number of individuals with perhaps as much as one-third of the population being affected.[1] A childhood and adolescent preponderance in disease risk has been found and prevalence rates are substantial almost irrespective of the geographical area of interest.[5]

Surveys that examine the causes of individual susceptibility to hay fever and associated atopic traits have consistently revealed a major impact of genetic factors in the aetiology. The correlation in liability between relatives exceeds what is observed among random sets of individuals from the population and even more so when relatives of increasing genetic relatedness are compared. Numerous, and to some extent, contradictory studies of atopic disease have ascribed the pattern of genetic transmission both to recessive, dominant, co-dominant and polygenic inheritance.[6] Additionally, a range of environmental influences are undoubtedly involved in the causal pathways of the disease, most likely in conjunction with an adverse genetic constitution.[7]

Studies of twins can provide useful information on the aetiology of complex respiratory phenotypes, such as hay fever. The classical twin study examines to what extent genetic and environmental factors contribute to the development of a disease. The rationale behind the classical twin study is that identical twins not only share all their genes, but also their upbringing and early environment. On the other hand, fraternal twins share, besides their upbringing and early environment, only 50% of their genes. Hence, if identical twins resemble each other more for a disease compared with fraternal twins, genetic factors are assumed to contribute to development of that disease.[8] Within the framework of the classical twin study it is possible to partition the causes for individual susceptibility to develop a certain disease into the effects of genes, family environment, and individual specific environment.[8] Studies that have addressed these issues have shown that the heritability of hay fever, i.e. the proportion of phenotypic variance ascribable to genes, is ranging from approximately 35% to 80%. Furthermore, familial aggregation of hay fever has been found to be much less due to environmental influences shared between family members, while unique environmental influences obviously are important when explaining individual differences in disease occurrence.[3,4,9,10] Studies arriving at these conclusions have mainly been conducted within children and young adolescent populations, while nationwide samples of young adults only have been studied to a limited extent.

In order to estimate the relative impact of genetic and environmental influences on individual susceptibility to hay fever we undertook a comprehensive nationwide questionnaire survey among young adult Danish twins.

Methods

Study design

The study population is based on the twin cohorts born between 1953 and 1982 in Denmark who were enroled in the nationwide Danish Twin Registry.[11] In these cohorts zygosity was established in 1991 using four questions of similarity and mistaken identity, which have a frequency of misclassification of less than 4%.[12] In 1994, a total of 34,076 twin individuals, who in 1991 have declared their willingness to participate in future studies, were sent a questionnaire with items aimed at identifying multiple phenotypes including hay fever and asthma.[13] The participation rate was 86%, comprising 29,183 subjects (12,356 intact twin pairs and 4471 single responders). Among the 12,356 intact pairs, a total of 11,750 pairs with complete data on zygosity and hay fever were identified and analyses were based on this sample. Subjects were regarded hay fever cases when responding affirmatively to

the question 'Do you have, or have you ever had hay fever?' A similar question was used to identify subjects with asthma.[13]

Statistical analysis

Assessment of twin pair resemblance for hay fever

Probandwise concordance rates and tetrachoric correlations assessed the degree of twin pair resemblance. The probandwise concordance rate denotes the probability that one twin has hay fever given the co-twin is affected, and is estimated as two times the number of concordant affected pairs (both twins are affected) divided by two times the number of concordant affected pairs plus the number of discordant pairs (one twin is affected).

Tetrachoric correlations are measures of similarity for dichotomous variables that estimate what the correlation would be if the variables were measured on a continuous scale. Tetrachoric correlations thus represent the correlation between hay fever in twin 1 and hay fever in twin 2 within a twin pair. They were estimated under the multifactorial threshold model. This model assumes that: (a) many factors (genetic and environmental) contribute to the development of the disorder; (b) each member of a twin pair is assumed to have his or her own liability, the pair of liabilities for a twin pair being assumed to be bivariate normally distributed; and (c) as the number of causal factors for the disorder increases in an individual, the liability for the disorder increases. When a threshold is reached the burden of liability becomes so great that disease (hay fever) results.[8] The threshold then represents the population prevalence of that disorder and is equivalent to a *z*-value of the (standard) normal distribution.[14] Age, and a history of asthma were included as covariates in the analyses. Both variables were incorporated into the threshold model allowing them to impact on the liability thresholds for hay fever according to their degree and direction of association with hay fever.

Variance components analysis

Latent factor models of genetic and environmental effects were fitted to the observed data, using maximum likelihood methods. These models assumed that the susceptibility to develop hay fever was a linear function of genetic and environmental influences. Genetic influences were partitioned into additive genetic effects (loci contributing additively to disease risk, A) and non-additive genetic effects (interacting alleles, either from the same locus-genetic dominance-or from separate loci-epistasis, D). Environmental influences were partitioned into shared environmental effects (environmental factors that increase the resemblance between members of the same family, C) and non-shared-random-environmental effects (influences unique to an individual, E).[8] For most human traits it is reasonable to assume all four sources of variance (A, D, C, and E) to act simultaneously. However, components C and D are not identified under the same model in studies that include only twins reared together.[15] Therefore, the likelihood of the data was determined under a saturated model that included components A, C, and E when there was evidence that shared environment influenced the disease susceptibility (MZ correlation below twice the DZ correlation) and under a saturated model that included components A, D, and E when there was evidence that genetic non-additivity influenced the disease susceptibility (MZ correlation above twice the DZ correlation). Nested sub-models were subsequently fitted by fixing to zero the appropriate variance components. The difference in log-likelihood between the saturated and the nested models provided an estimate of the significance of the contribution of the individual variance components to the disease susceptibility. Additionally, we considered the fit of models that included tests for equal magnitudes of genetic effects across sexes and sex-limitation of genetic effects. A P-value <0.05 was considered to be statistically significant. The statistical package Mx was used for the analyses.[16] The protocol was evaluated and approved by the Scientific Ethics Committee.

Results

The distribution of hay fever according to zygosity is shown in Table 1. The mean age of the cohort was 26.5 years (age-range 12–41 years) and 52% were females. The cumulative (lifetime) prevalence of hay fever was the same across the different zygosity groups with an overall rate of 12.6%. The probandwise concordance rates and tetrachoric correlations for identical twins were significantly higher and about twice that for fraternal twins, indicating genetic influences on disease aetiology. We found no statistically significant effect of age on the estimates ($P = 0.71$), whereas a history of asthma was significantly associated with hay fever ($P < 0.001$).

Table 2 shows the results from variance components analysis. In both sexes models that included

Table 1 Cumulative prevalence and correlation measures for hay fever in a sample of 11,750 twin pairs, 12–41 years of age.

Zygosity group	Pairs (*n*)	Hay fever (*n*)	Prevalence (%)	Discordant pairs (*n*)	Concordant pairs (*n*)	C_{Pr} (95% CI)	Tetrachoric correlations (95% CI)
MZ	3723	940	12.6	454	243	0.52 (0.48–0.56)	0.72 (0.69–0.76)
Males	1697	416	12.3	188	114	0.55 (0.49–0.61)	0.77 (0.70–0.82)
Females	2026	524	12.9	266	129	0.49 (0.44–0.55)	0.69 (0.62–0.74)
DZ-ss	4358	1081	12.4	795	143	0.26 (0.23–0.30)	0.34 (0.27–0.40)
Males	2127	537	12.6	385	76	0.28 (0.23–0.34)	0.37 (0.27–0.45)
Females	2231	544	12.2	410	67	0.25 (0.20–0.30)	0.31 (0.21–0.40)
DZ-os	3669	938	12.8	732	103	0.22 (0.18–0.26)	0.23 (0.16–0.31)
Males		465	12.7	362*			
Females		473	12.9	370*			
All DZ	8027	2019	12.6	1527	246	0.24 (0.22–0.27)	0.29 (0.24–0.34)
Total	11,750	2959	12.6	1981	489	0.33 (0.31–0.35)	0.46 (0.42–0.49)

C_{Pr}, probandwise concordance rate.
Abbreviations: MZ, monozygotic; DZ-ss, dizygotic same sex; DZ-os, dizygotic opposite sex.
*Males and females being the affected twins, respectively.

Table 2 Variance components analysis of hay fever in a sample of 11,750 twin pairs, 12–41 years of age.

Model	Variance components			Fit statistics		
	A	D	E	$\Delta -2\log Q$	Δdf	*P*-value
Males						
ADE	0.71 (0.33–0.81)	0.06 (0.00–0.45)	0.23 (0.18–0.30)			
AE	0.76 (0.70–0.81)	—	0.24 (0.19–0.30)	0.09	1	0.77
DE	—	0.78 (0.72–0.83)	0.22 (0.17–0.28)	13.21	1	<0.001
E	—	—	1.00	330.80	2	<0.001
Females						
ADE	0.55 (0.15–0.73)	0.14 (0.00–0.55)	0.31 (0.25–0.38)			
AE	0.68 (0.62–0.74)	—	0.32 (0.26–0.38)	0.50	1	0.48
DE	—	0.70 (0.64–0.76)	0.30 (0.24–0.36)	7.42	1	0.006
E	—	—	1.00	291.41	2	<0.001

Standardized parameter estimates (95% confidence intervals) of additive genetic factors (A), non-additive genetic factors (D), and non-shared environmental factors (E).
$\Delta -2\log Q$, difference in model fit (log-likelihood) between saturated model and nested model.
Δdf, difference in degrees of freedom between saturated model and nested model.

effects of additive genetic factors and non-shared environmental factors (AE-models) best described individual susceptibility to hay fever. Parameter estimates were not significantly different in males compared with females, with genes accounting for 71% and non-shared environmental factors accounting for 29% of the individual susceptibility to hay fever. The same genes contributed to the susceptibility to hay fever both in males and in females, $P = 0.10$.

Additional variance components analysis was performed for hay fever both in families with and in families without asthma ('sporadic' hay fever). These analyses showed that the liability to hay fever in families with asthma was ascribable both to additive genetic factors (36%), shared environment (57%), and non-shared environment (11%), whereas the susceptibility to 'sporadic' hay fever could be attributed solely to additive genetic factors (70%) and non-shared environment (30%).

Discussion

We infer from our study that the susceptibility to develop hay fever is influenced mainly by individual

genetic differences between people. Furthermore, a substantial portion of the susceptibility to hay fever is due to individual differences in environmental exposures. Additionally we found that, in besides genes, environmental exposures shared between members of the same family—for example upbringing and early life environment—are important for development of hay fever in families where asthma is also present. On the contrary, the susceptibility to develop 'sporadic' hay fever seems to be ascribable mainly to individual genetic differences with no impact of shared environment.

These results expand upon earlier findings from four Scandinavian[4,9,10,17] and one Australian[3] questionnaire-study among twins, which all emphasise that most of the familial resemblance of hay fever is due to genetic factors. In particular, Duffy and co-workers found a heritability of hay fever of 60% in a study among 3808 twin pairs, 18–88 years of age (mean age 36.5 years) ascertained from the Australian Twin Registry.[3] Furthermore, a study by Lichtenstein and Svartengren of 1480 twin pairs, 7–9 years of age, from the Swedish Twin Registry, showed that the susceptibility to develop hay fever was ascribable to 33% additive genetic effects in boys compared with 70% in girls.[4] Finally, in a study that comprised 1765 Finnish adolescent twin pairs the estimate of additive genetic variance was around 80%.[9] Several other studies confirm these findings by showing that concordance rates for hay fever in identical twins are significantly higher than in fraternal twins,[10] even when the twins have been reared apart.[18] We tested for sex-limitation of genetic effects and found no differential expression in males compared with females. This assumption was also tested in the Australian study and could neither be demonstrated in that population.[3]

Acknowledging the imprecise definition of hay fever in epidemiological studies, several surveys have examined the quantitative genetics of hay fever intermediate phenotypes within twin populations. These studies have mainly focussed on objective measures of disease such as skin test reactivity and levels of serum IgE, which are assumed to be more accurate measures of disease. These studies consistently confirm a substantial genetic component and a negligible contribution from common familial environment in the aetiology of atopy.[18–20] Moreover, these intermediate phenotypes are not biased by imprecise subjective categorisations of disease status and are inherently more informative and statistically powerful than binary clinical definitions of atopy, such as hay fever.[6] These advantages have been exploited in the course for mapping susceptibility loci for atopic traits[7] and additionally, a few studies have tried to address binary hay fever correlates such as allergic rhinitis in a genome-wide linkage setting, confirming that a large number of candidate loci are likely involved in the disease process.[21,22]

The magnitude of affectedness in this sample was somewhat lower than that found in the general singleton population.[1] That is, we found cumulative prevalence rates of around 12%, which, however, is considerably lower than the prevalence rate of 30% found among Australian twins.[3] Furthermore, unlike other studies that have reported an excess risk among women,[3] we found equal prevalence rates in the two sexes. Whether this reflects geographical differences rather than just a low prevalence among European twins remains debatable, but nevertheless our finding of a lower prevalence in twins compared with that found among singletons is in line with some earlier reports of a reduced prevalence of atopic diseases in twins. According to the 'hygiene hypothesis', as argued by Strachan et al.[23] twin sib-ships, i.e., having an extra sibling of the same age, could be a special case of large family size conferring a protective effect on allergic disease.

One limitation of the present study is that we only relied on the validity of one question, i.e. 'Do you have, or have you ever had hay fever?' to detect the presence or absence of the disease. We recognise that this procedure is a crude approximation of a phenotype that follows various developmental trajectories and presumably is understood differently among different individuals.[2] A phenomenon that would seem to be especially pronounced in this study since it covers an age-range of participants of almost 30 years. That leaves a potential for inaccurate estimates of the disease risk owing to recall bias among subjects being affected only in childhood as well as among those with present disease due to differences in perception of symptoms. Nevertheless, at the expense of an inaccurate diagnosis we infer our conclusions on the basis of an extensive sample of subjects, who were selected from a population-based registry and hence the study is not biased by non-random recruitment through media advertising and volunteer campaigns, as can be seen in twin registries outside the Scandinavian countries.[3,20]

We conclude that identical twins are more likely to be concordant for hay fever than are fraternal twins, which indicates a genetic contribution to disease aetiology. Biometrical modelling suggested that around three-fourths of the individual differences in susceptibility to develop hay fever are ascribable to genetic effects operating in an additive fashion with the rest being due to individual differences in environmental exposures.

Our results furthermore indicated that the liability to develop hay fever in families where asthma is also present to a great extent is due to influences from family environment and upbringing, whereas 'sporadic' hay fever mainly develops because of individual differences in genetic vulnerability. These results add new insight into the origins of hay fever and indicate that different sub-forms of hay fever may be aetiologically different. Further research is needed to clarify to what extent clinical heterogeneity within atopic disease can be attributed to genetic and/or environmental causes.

Acknowledgement

We thank Axel Skytthe, M.Sc., Ph.D., from The Danish Twin Registry for an invaluable help with the management of the data.

References

1. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol* 2001;**108**(1 Suppl.):S2–8.
2. Zacharasiewicz A, Douwes J, Pearce N. What proportion of rhinitis symptoms is attributable to atopy? *J Clin Epidemiol* 2003;**56**(4):385–90.
3. Duffy DL, Martin NG, Battistutta D, Hopper JL, Mathews JD. Genetics of asthma and hay fever in Australian twins. *Am Rev Respir Dis* 1990;**142**(6 Part 1):1351–8.
4. Lichtenstein P, Svartengren M. Genes, environments, and sex: factors of importance in atopic diseases in 7–9-year-old Swedish twins. *Allergy* 1997;**52**(11):1079–86.
5. ISAAC Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998;**351**(9111):1225–32.
6. Palmer LJ, Cookson WOCM. Atopy and asthma. In: Bishop T, Sham P, editors. *Analysis of multifactorial disease*. Oxford: BIOS; 2000. p. 215–37.
7. Mathias RA, Freidhoff LR, Blumenthal MN, et al. Collaborative Study of the Genetics of Asthma (CSGA). Genome-wide linkage analyses of total serum IgE using variance components analysis in asthmatic families. *Genet Epidemiol* 2001;**20**(3):340–55.
8. Neale MC, Cardon LR. *Methodology for genetic studies of twins and families*. Dordrecht, The Netherlands: Kluwer Academic Publishers; 1992.
9. Rasanen M, Laitinen T, Kaprio J, Koskenvuo M, Laitinen LA. Hay fever—a Finnish nationwide study of adolescent twins and their parents. *Allergy* 1998;**53**(9):885–90.
10. Edfors-Lubs M. Allergy in 7000 twin pairs. *Acta Allergol* 1971;**26**:249–85.
11. Kyvik KO, Green A, Beck-Nielsen H. The new Danish Twin Register: establishment and analysis of twinning rates. *Int J Epidemiol* 1995;**24**:589–96.
12. Christiansen L, Frederiksen H, Schousboe K, et al. Age- and sex-differences in the validity of questionnaire-based zygosity in twins. *Twin Res* 2003;**6**(4):275–8.
13. Skadhauge LR, Christensen K, Kyvik KO, Sigsgaard T. Genetic and environmental influence on asthma: a population-based study of 11,688 Danish twin pairs. *Eur Respir J* 1999;**13**: 8–14.
14. Posthuma D, Beem AL, de Geus EJ, et al. Theory and practice in quantitative genetics. *Twin Res* 2003;**6**(5): 361–76.
15. Keller MC, Coventry WL. Quantifying and addressing parameter indeterminancy in the classical twin design. *Twin Res* 2005;**8**(3):201–13.
16. Neale MC, Boker SM, Xie G, Maes HHM. *Mx statistical modeling*, 6th ed. Richmond, VA, USA: Department of Psychiatry; 2003.
17. Nystad W, Roysamb E, Magnus P, et al. A comparison of genetic and environmental variance structures for asthma, hay fever and eczema with symptoms of the same diseases: a study of Norwegian twins. *Int J Epidemiol* 2005;**34**(6): 1302–9.
18. Hanson B, McGue M, Roitman-Johnson B, Segal NL, Bouchard Jr TJ, Blumenthal MN. Atopic disease and immunoglobulin E in twins reared apart and together. *Am J Hum Genet* 1991;**48**(5):873–9.
19. Hopp RJ, Bewtra AK, Watt GD, Nair NM, Townley RG. Genetic analysis of allergic disease in twins. *J Allergy Clin Immunol* 1984;**73**(2):265–70.
20. Strachan DP, Wong HJ, Spector TD. Concordance and interrelationship of atopic diseases and markers of allergic sensitization among adult female twins. *J Allergy Clin Immunol* 2001;**108**(6):901–7.
21. Barnes KC, Freidhoff LR, Nickel R, et al. Dense mapping of chromosome 12q13.12-q23.3 and linkage to asthma and atopy. *J Allergy Clin Immunol* 1999;**104**(2 Part 1):485–91.
22. Haagerup A, Bjerke T, Schoitz PO, Binderup HG, Dahl R, Kruse TA. Allergic rhinitis—a total genome-scan for susceptibility genes suggests a locus on chromosome 4q24-q27. *Eur J Hum Genet* 2001;**9**(12):945–52.
23. Strachan DP, Moran SE, McInneny K, Smalls M. Reduced risk of hospital admission for childhood asthma among Scottish twins: record linkage study. *BMJ* 2000;**321**:732–3.